Muscular dystrophies in Arab countries

Fayçal Hentati, MD
National Institut of Neurology
Tunis - TUNISIA

Autosomal Recessive Limb-Girdle Muscular Dystrophies [LGMD2]

- Primary and progressive muscle disorders usually affecting predominantly the pelvic and then the scapular girdle.
- Autosomal recessive inheritance.
- 11 genes identified : LGMD 2A-2K
- Pathogenic mechanism leading to muscle necrosis unknown.
- Relation between the different proteins involved remains unknown except for the sarcoglycanopathies.

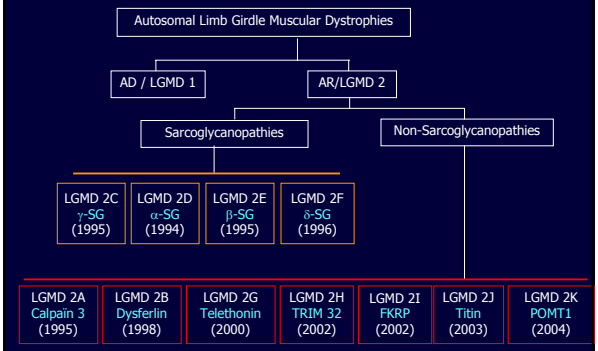
Historical background

Since 19 century: families with AR DLMD reported in Europe, Japan and USA

1977-83 Clinical, epidemiological and muscle biopsy of Duchenne-like MD affecting both sexes and frequent in Tunisia [Ben Hamida et al]

1987 Cloning of the dystrophin gene: *starting point of the molecular study of AR LGMDs* [Kunkel et al]

1989-*2003* α and γ–SG genes identifications on Tunisian, Lebanese and Algerian families (1992-96)
LGMD 2F - δ-*SG gene* identification on Brazilian families
LGMD 2B -Myoshi gene identification (dysferlin) on Palestinian and Tunisian families (1995-1998)
Mapping of the gene of LGMD2I on Tunisian family (2001)



High prevalence of AR LGMD in Arab Countries

Social and cultural conditions

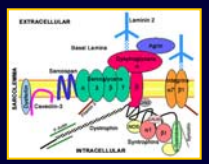
- High rate of consanguineous marriage: 36-60%
- Large sibship size: 5.3 to 7.4
- Improvement of public health indicator:
  - Decrease of infantile mortality
  - Increase of life expectancy
  - Decrease of malnutrition and infectious diseases
- Improvement of neurological expertise

Reported Muscle disorders

Muscular Dystrophies:
- Duchenne muscular dystrophies
- Sarcoglycanopathies.
- Miyoshi MD, LGMD 2B
- LGMD 2I
- Congenital Muscular dystrophies
- Hereditary Inclusion Body Myopathies

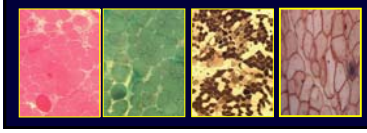
The Sarcoglycans

- Sarcoglycans: N-glycosylated transmembrane proteins
- Exclusively expressed in cardiac and skeletal muscle
- Form a tetrameric complex at the muscle cell plasma membrane.
  ⇒ stabilizes association of dystrophin with dystroglycans and contributes to the stability of the plasma membrane.
- Four sarcoglycan genes α, β, γ and δ-SG related to each other structurally and functionally.
- Four distinct genetic forms :
  - LGMD2C: γ-sarcoglycan gene (chr13q).
  - LGMD2D: α-sarcoglycan gene (chr17q)..
  - LGMD2E: β-sarcoglycan gene. (chr4q).
  - LGMD2F: δ-sarcoglycan gene, (chr5q).



The Sarcoglycanopathies
Clinical phenotype

- Early-childhood onset.
- Progressive course.
- Muscle weakness and atrophy affecting pelvic followed by shoulder muscle.
- Frequent calves hypertrophy.
- Variable course between siblings with severe Duchenne-like course (wheelchair-bound before 13) to mild course (patients ambulant later than 16 years).
- High CK rate
- Dystrophic feature on muscle biopsy



Sarcoglycans expression

When 1 mutation is present in one of SG-gene :

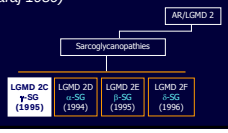
- The protein encoded by that gene is usually absent
- Secondary and variable reduction in the other SG

Sarcoglycan expressions in a γ-sarcoglycanopathy [LGMD2C]

γ- sarcoglycanopathies
LGMD2C Epidemiological Data

- Rare in European population (LGMD2D >LGMD2C 8:2 ratio)
- Most frequent LGMD2 in Tunisia: 81% of sarcoglycanopathies ; 75 % of all LGMD2
- Similar prevalence than DMD in Tunisia: 1/3500 children
- Reported in:

Algeria	(Masmoudi 1986; Azibi 1992)
Morocco	(El Kerch 1992)
Egypt	(Hachem 1982)
Saudi Arabia	(Salih and Bohliga)
Kuwait	(Faraj 1989)

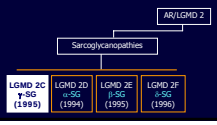


γ-sarcoglycanopathy : LGMD 2C
Molecular genetic findings in Tunisia

- Linkage to chromosome 13q12
- Linkage disequilibrium with D13S232 marker.
- 1 out of 20 known mutations found in about 99% of Tunisian patients: del521-T mutation.
- The same mutation was reported in other Arab countries

➔ *Presence of a founder effect*

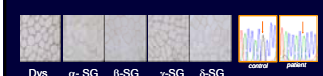
- 582insA mutation first reported in one Libyan family and found in a Tunisian family

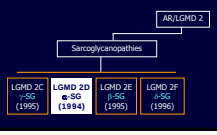


α-Sarcoglycanopathy - LGMD 2D
in Arab Countries

LGMD2D: α-sarcoglycan gene (chr17q).

- The most frequent Sarcoglycanopathy in Europe(LGMD2D >LGMD2C 8:2)
- Rarely documented in Arab countries.
- Scarcity of publications in Arab countries populations
- Severe to mild phenotype
- 10% of families in Tunisia.
- Various mutation in Tunisian families without founder effect
- New mutation found in a Tunisian family (190G>A) out of 108 reported mutations.

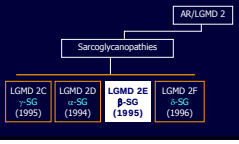




β - Sarcoglycanopathy – LGMD 2E

LGMD2E: β-sarcoglycan gene. (chr4q).

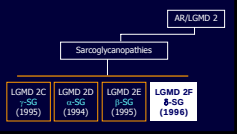
- **Less frequent than LGMD 2D (LGMD2D/LGMD2E=8/4) and more frequent than LGMD 2C (LGMD2D/LGMD2C=8/2) in outbreed populations (26 reported mutations).**
- **Small families or isolated patients with widespread geographic origins.**
- **Reported in only one Tunisian family with homozygous missense mutation (G276T) in exon 3**
- **Reported in Sudan (Salih et al).**
- **Absence of sarcoglycan expression in muscle biopsy**
- **Severe phenotype**



δ – sarcoglycanopathies - LGMD 2F

- The rarest sarcoglycanopathy (1/8 compared to LGMD2D)
- Majority of the patients from Brazil (severe phenotype)

Not reported in Arab countries



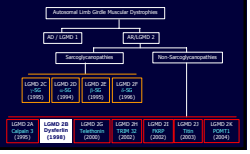
LGMD 2B/Dysferlinopathy
Miyoshi Muscular Dystrophy

1987 Report of a distal muscular dystrophy in Japan.

1992 Report of one Palestinian family with mild course AR LGMD

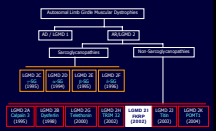
1995 Linkage of MM to chr. 2p12 in one Tunisian family (Bejaoui *et al.)*
Linkage of LGMD 2B on chr. 2p12 (Bashir *et al)*

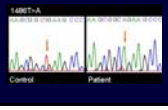
1998 Identification of the LGMD 2B gene (Bashir *et al)*
and of MM (Liu *et al):* the dysferlin gene, 55 exons
Mutations identified in Palestinian families and not yet in Tunisian families



LGMD 2I

- Genetic form fist described in Tunisian family (Driss et al 2001).
- The most frequent LGMD2 in Europe
- Remains rare in Tunisia.
- Variable age of onset between 1.5 to 27 yrs
- Proximal limb muscle weakness predominantly affecting the pelvic girdle
- Variable course
- High CK rate
- Muscle biopsy: Dystrophic changes
- Linkage to chr. 19q13.3
- Gene : FKRP gene. (allelic to CMD1C).





Unresolved aspects of LGMD 2

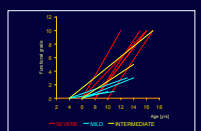
Intrafamilial phenotypic variability

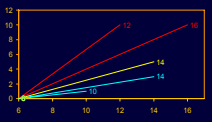
Epidemiological repartition: one predominant form (LGMD 2C)and one predominant mutation del521 with founder effect.

Genetic counseling : intrafamilial genetic heterogeneity

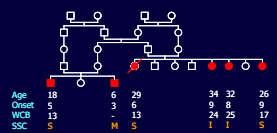
Intrafamilial phenotypic variability

Phenotypic distribution of
LGMD 2C deltaT521 patients (128 patients)





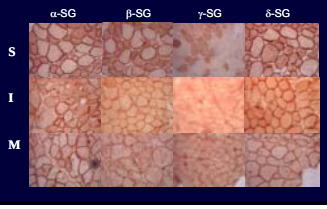
	Nb patients	Age exam.	Age onset	Age WCB
Severe	46.9% *(n=62)*	20.8 ± 7.2	6.1 ± 2.4	14 ± 2.1
Intermediate	28.8% *(n=38)*	23.8 ± 6.9	6.0 ± 2. 4	17.8 ± 3.3
Mild	24.2% *(n=32)*	21.6 ± 9.9	6.2 ± 2.4	22.7 ± 8.5
Total	*100%*	*21.9 ± 8.0*	*6.1 ± 2.4*	*16.3 ± 4.9*



Intrafamilial phenotypic variability

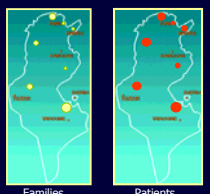
- Clinical variability between siblings is not related to:
  - Age of onset
  - Sarcoglycan expressions
  - Environmental factors: 75 % of families displayed inter-siblings variability.
- Probably related to a modifier gene controlling the severity.

Sarcoglycan subunits expression in LGMD 2C



Epidemiological repartition: one predominant form (LGMD 2C)and one predominant mutation del521 with founder effect

Distribution of del 521Tmutation in Arab countries



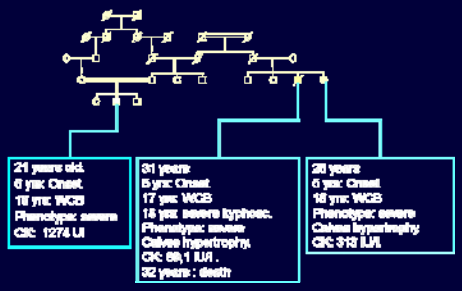
- LGMD2C:Most frequent AR LGMD in Tunisia: 81% of sarcoglycanopathies 75 % of all LGMD2
- 1 out of 20 known mutations found in about 99% of Tunisian patients: del521-T mutation

One predominant form (LGMD 2C) and one predominant mutation del521 with founder effect

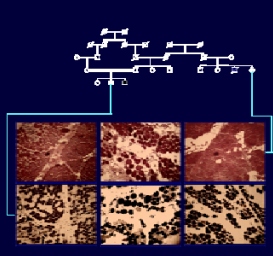
- High prevalence not explainable by mutational rate ≠ DMD
- Disabling disease incompatible with the presence of patient's progeny: other forms of sarcoglycanopathies remain rare despite high rate of consanguineous marriages
- Distribution correspond to Arabic flux migration
- Presence of a founder effect ≠ genetic heterogeneity of other sarcoglycanopathies.
- Selective advantage of del del521T in γ-SG heterozygote ?

Genetic Counseling: Intrafamilial Genetic heterogeneity

Genetic Counseling: Intrafamilial Genetic heterogeneity

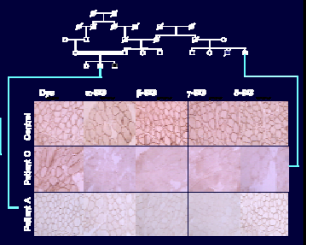


Muscle biopsy: histoenzymological staining



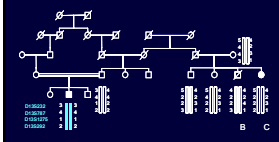
Similar dystrophic changes

Muscle biopsy: immunostaining

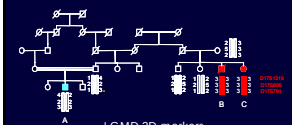


Distinct sarcoglycan expressions

Genetic linkage

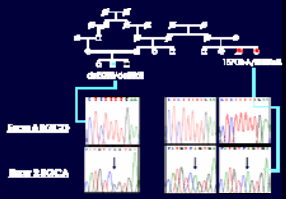


LGMD 2C markers



LGMD 2D markers

Mutation analysis

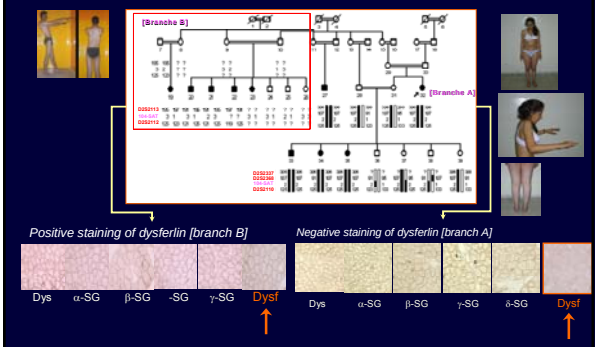


Involvement of two distinct genes defects:
LGMD 2C (homozygous del525T)
LGMD 2D [homozygous 157G>A]

Phenotypic homogeneity and genetic heterogeneity : How?

- Patients share a common ancestor
- They displayed
  - Similar severe LGMD clinical feature
  - Close dystrophic muscle biopsy findings
- There was variable muscle sarcoglycans expression
- Involvement of two distinct genes defects:
  - LGMD 2C (homozygous del525T)
  - LGMD 2D [homozygous 157G>A]

Genetic heterogeneity was not an isolated phenomenon



Phenotypic homogeneity and genetic heterogeneity : *What does it mean ?*

- Two comments:
  - 1. Difficulty of genetic counseling in inbreed populations :
    - Paradigm that patients from the same family sharing the same ancestor and similar phenotype carry the same genetic disorder and the same mutation no more accepted ?
    - Need to analyze all affected patients within families before giving genetic counseling .
  - 2. Significance of such association:
    - coincidental association is the most logical hypothesis
    - but does this hypothesis have statistical basis ?

Conclusion (1)

- Arab patients had contributed in the identification of a number of genetic forms of LGMD2.
- Some LGMD2 forms are frequent in Arab populations (γ SG) whereas others seem to be rare, although the high rate of consanguineous marriage.
- Large predominance of one mutation with a founder effect in the most frequent form (LGMD 2C) whereas there are various mutations (family private mutations)in rare genetic forms.

Conclusion (2)

- The basis of this epidemiological pattern remain unknown (selective advantage?).
- Variable phenotypes in patients sharing the same mutation is frequent and could be related to a modifier gene.
- despite the presence of one predominant mutation, the presence of genetic heterogeneity in consanguineous families complicates the genetic counseling.
- Developing a DNA diagnosis ships including all LGMD2 mutations found in Arab population may be the solution for genetic screening.